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The Use of Multivitamin/Multimineral Supplements: A Modified Delphi Consensus Panel Report

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ABSTRACT

Purpose: Evidence supporting the use of dietary supplements, in particular, multivitamin/multimineral supplements (MVMS), has been mixed, complicating the ability of health care professionals to recommend their use. To clarify the role that MVMS can play in supporting human health, a series of consensus statements was developed based on expert opinion.

Methods: A panel of 14 international experts in nutritional science and health care was convened to develop consensus statements related to using MVMS in supporting optimal human health. The modified Delphi process included 2 rounds of remote voting and a final round of voting at a roundtable meeting where evidence summaries were presented and discussed. The level of agreement with each of 9 statements was rated on a 5-point Likert scale: agree strongly; agree with reservation; undecided; disagree; or disagree strongly. Consensus was predefined as

≥80% of the panel agreeing strongly or agreeing with reservation to a given statement.

Findings: Consensus was reached for all statements. The panel determined that MVMS can broadly improve micronutrient intakes when they contain at least the micronutrients that are consumed insufficiently or have limited bioavailability within a specified population. MVMS formulations may also be individualized according to age, sex, life cycle, and/or other selected characteristics. There are specific biological processes and health outcomes associated with deficient, inadequate, and adequate micronutrient levels. Adequate intake is necessary for normal biological functioning required for good health; in some instances, higher

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than recommended micronutrient intakes have the potential to provide additional health benefits. Meeting daily intakes established by dietary reference values should be an explicit public health goal for individuals and populations. Use of MVMS is one approach to ensure that adequate micronutrient needs are met in support of biological functions necessary to maintain health. Long-term use of MVMS not exceeding the upper limit of recommended intakes has been determined to be safe in healthy adults. There is insufficient evidence to indicate that MVMS are effective for the primary prevention of chronic medical conditions, including cardiovascular disease and cancer. However, for certain otherwise healthy subpopulations (eg, pregnant women, older adults) and some individuals with existing medical conditions who experience inadequacies in micronutrient intake, addressing inadequacies by using MVMS can provide health benefits.

Implications: This consensus panel has described key issues related to the use of MVMS among individuals at risk of or presenting with inadequacies in micronutrient intake or biomarker status. (*Clin Ther.* 2018;40:640–657) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: adverse effects, Delphi consensus, dietary supplements, health benefits, multivitamin/multimineral supplements, nutrition.

INTRODUCTION

Dietary supplements and, in particular, multivitamin/multimineral supplements (MVMS), are widely used¹; recent data from the United States suggest that the use of MVMS is declining, however.^{1,2} No guidelines currently exist for recommending the use of MVMS, and nutritional education and training among health care professionals (HCPs), including physicians, nurses, and pharmacists, are limited.^{3–7} Thus, little direction is available for HCPs to guide patients in this area. Results from randomized controlled trials (RCTs) conducted with MVMS provide conflicting evidence about their potential benefits in preventing/treating chronic medical conditions (CMCs), leading some to question their value, particularly in higher income countries.^{8,9} Nonetheless, there is ample evidence from national dietary intake surveys reporting deficiencies and inadequacies in micronutrient intake

and/or status, and correcting these deficiencies can have health benefits.^{10,11} To address this conundrum, an international panel of experts in the areas of nutritional science and health care was convened to develop consensus statements that discuss issues regarding MVMS use.

An essential component in discussing the role of dietary supplements involves defining recommended intakes for maintaining good health. Vitamin and mineral requirements are defined as the intake needed to meet a specified indicator of adequacy for each nutrient.¹² The terms commonly used to describe reference intakes are defined in [Figure 1](#).¹³ However, it is important to appreciate that dietary reference values can vary among countries or regions based on different criteria and/or approaches to reach consensus.

MATERIALS AND METHODS

An international group of 14 experts in nutritional science and health care was convened to develop a series of consensus statements that present guidelines for using MVMS. To ensure that the panel was composed of a heterogeneous group of experts in the specialty area and to provide global representation that would allow for regional variations to be accounted for in the statements, the consensus panel's co-chairs (J.B.B. and H.C.) identified a select number of participants based on their expertise and geographic location beginning in November 2016. After initially contacting the co-chairs, the sponsor (Pfizer Consumer Healthcare, Madison, New Jersey) had no involvement in conducting the consensus panel or preparing the present article.

Once participants were identified, the co-chairs developed a set of initial questions related to using MVMS. Each assigned panel member, as selected by the co-chairs, began searching the literature and identifying information sources to address these questions. Where applicable, the methods for conducting literature reviews are described in the corresponding evidence summaries. After reviewing the literature, panelists selected as Statement Leads developed initial drafts of each statement, which were shared with team members chosen by the co-chairs to assist in this effort. The initial 9 statements were then circulated to the entire panel for a first round of remote consensus voting. The voting followed a modified Delphi process,^{14,15} in which the level of agreement

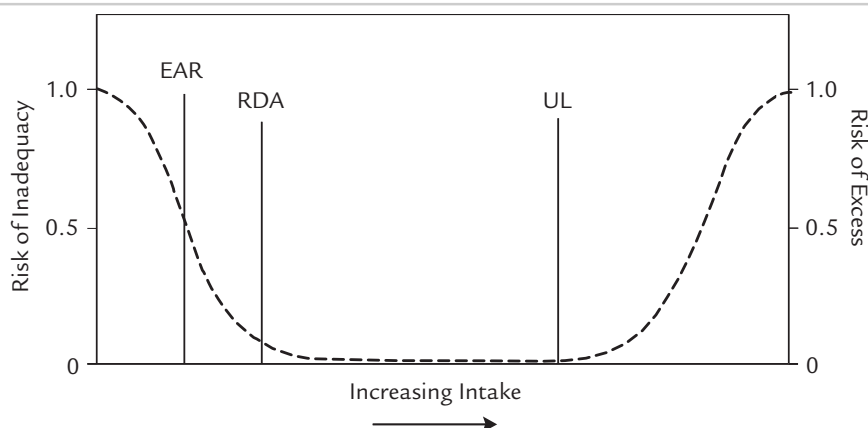


Figure 1. Definitions of terms used to describe components of Dietary Reference Intakes.¹¹ This figure shows that the Estimated Average Requirement (EAR) is the intake at which the risk of inadequacy is 0.5 (50%) for an individual. The Recommended Dietary Allowance (RDA) is the intake at which the risk of inadequacy is very small, only 0.02 to 0.03 (2% to 3%). The Adequate Intake (AI) does not bear a consistent relationship to the EAR or the RDA, because it is set without the estimate of the requirement. As a result, the AI is not included in this figure. At intakes between the RDA and the Tolerable Upper Intake Level (UL), the risks of inadequacy and excess are both close to 0. At intakes above the UL, the risk of adverse effects may increase. AI is the recommended average level of daily nutrient intake based on observed or experimentally determined approximations of intake by a group (or groups) of apparently healthy people that are assumed to be adequate; it is used when an RDA cannot be determined. Mean usual intake at or above this level has a low probability of inadequacy among individuals or groups. When the AI for a nutrient is not based on mean intakes of healthy populations, the assessment of adequacy is made with less confidence. EAR is the average daily nutrient intake level estimated to meet the requirement of one half the healthy individuals in a particular life stage and sex group; it is used to examine the probability that usual intake is inadequate in an individual or to estimate the prevalence of inadequate intakes within a group. Provided certain assumptions are met, the prevalence of inadequate intakes in a group can be estimated as the percentage of the group's usual intake distribution that falls below the EAR. The RDA is the average daily nutrient intake level that is sufficient to meet the nutrient requirement of nearly all (97%–98%) healthy individuals in a particular life stage and sex group. For nutrients with normal requirement distributions, the RDA is calculated from the EAR by adding 2 SDs of the requirement distribution to the EAR. Usual intake at or above the RDA has a low probability of inadequacy for an individual; it is not to be used to assess intakes of groups. The UL is the highest average daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases. Usual intake above this level may place an individual at risk of adverse effects from excessive nutrient intake; it is used to estimate the percentage of the population at potential risk of adverse effects from excessive nutrient intake. Adapted with permission of National Academies Press from *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academies Press; 2000; permission conveyed through Copyright Clearance Center, Inc.

was rated on a 5-point Likert scale: agree strongly (A+); agree with reservation (A); undecided (U); disagree (D); or disagree strongly (D+). Consensus was predefined as $\geq 80\%$ of the panel rating a given statement A+ or A.

After the Statement Leads and their team members revised the statements, a subsequent round of remote

voting was conducted; the final round of voting was conducted at an in-person meeting of all panelists in Philadelphia, Pennsylvania, in June 2017, where the Statement Leads presented evidence summaries used to support their statements. The live meeting, which was moderated by the co-chairs, was included to allow the panel members to openly discuss the statements. The

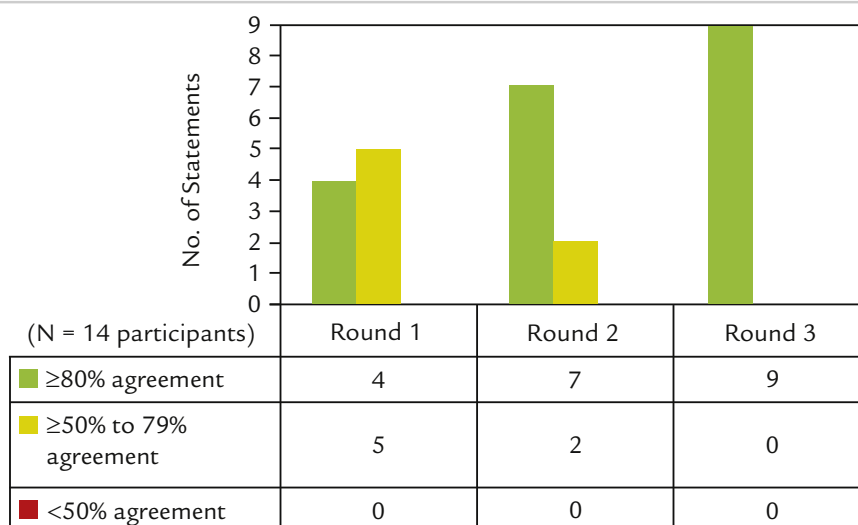


Figure 2. Evolution of consensus voting over 3 rounds.

meeting was followed by the final round of anonymous voting using an automated response system.¹⁶ The co-chairs decided to forego rating the quality of evidence and strength of recommendations because these criteria would not be applicable to most statements; where applicable, the quality of evidence is informally described. A summary of the consensus voting is presented in Figure 2.

RESULTS

Consensus was reached for all statements. Upon completion of the in-person meeting, a confidential poll was conducted and panel members agreed that no commercial bias was evident in the process before or during the meeting. Also, all participants provided adequate input on all statement ratings and recommendations, which are described individually in the following sections.

1. For the purpose of broad-spectrum micronutrient supplementation for a general population, MVMS should contain at least the micronutrients that are commonly underconsumed relative to their recommended intakes within that country/region. Most of these vitamins and nutritionally essential minerals should be present in amounts approximating recommended intakes. Within this context, MVMS may be safely formulated for large subgroups according to age, sex, and/or life-cycle-specific micronutrient needs.

A+: 64%; A: 36%

There is currently neither consensus nor published criteria quantifying the doses of micronutrients that should be included in MVMS. However, several definitions of MVMS have been proposed. For example, the US National Institutes of Health defines MVMS as: “any supplement containing 3 or more vitamins and minerals but no herbs, hormones, or drugs, with each component at a dose less than the Tolerable Upper Intake Level (UL) determined by the Food and Nutrition Board—the maximum daily intake likely to pose no risk for adverse health effects.”¹⁷ The National Institutes of Health classifies MVMS into subgroups as: (1) “once daily,” which contain most or all vitamins and essential minerals at levels approximating the Recommended Dietary Allowance (RDA) or Adequate Intake (AI); (2) special formulations designed for specific subpopulations, and packs containing multiple individual supplements; and (3) “specialized” formulations that might contain vitamins and minerals at levels substantially above the RDA and sometimes the UL.¹⁸ In contrast, others have defined MVMS as dietary supplements providing ≥100% of the RDA or AI for ≥9 to 10 vitamins and nutritionally essential minerals.^{2,10,11} Currently available MVMS do not generally contain the RDA or AI for calcium, choline, magnesium, potassium, vitamin K, phosphorus, and others.

Evidence from international databases, review articles, and national population-based surveys indicates that micronutrient intake deficiencies/inadequacies

(especially for vitamin A, iron, iodine, folate, and other B vitamins, vitamins D and E, magnesium, and calcium) occur on a global scale and are mirrored by low intakes from foods and supplements.^{10,19–27} Despite the absence of established regulatory and scientific definitions for MVMS, there is agreement that these products should minimally contain the vitamins and minerals that are commonly underconsumed relative to their RDA or AI within a country/region in amounts below the UL. In addition, MVMS may be safely formulated for specific subgroups according to age, sex, and/or life-cycle-specific micronutrient needs. The decision by HCPs to recommend MVMS can be individualized based on a person's diet and risk for nutrient deficiencies/inadequacies.²⁸ Importantly, MVMS are considered to be supplements, not substitutes, for a balanced diet. Indeed, MVMS are generally perceived by consumers as an “insurance policy” to help achieve adequate micronutrient intake. MVMS that maintain intake at or below the RDA or AI are unlikely to result in excess intake, even when including the contribution of diet and fortification, although use of additional supplements might increase the risk of exceeding the UL.^{11,29–31}

2. Several factors are associated with deficient, inadequate, or adequate micronutrient intake: biological functions; cellular, metabolic, or physiological states; and health outcomes. For some micronutrients, higher intakes might provide added health benefits.

A+: 50%; **A:** 50%

Micronutrients have distinct biological functions, including serving as essential co-factors to many enzymes and as structural elements of biological macromolecules (eg, B vitamins and DNA synthesis), involvement in one-carbon metabolism, and acting as hormones and antioxidants.^{32–35} These biological functions are essential to metabolic functioning, growth and development, and many cellular and organ system functions. In most cases, RDAs and AIs are based on specific biological or physiological indicators for each micronutrient to prevent deficiency diseases/syndromes. For example, Dietary Reference Intakes (DRIs) of vitamin D and calcium are intended to promote bone mineral density in adolescents and reduce loss with aging, and those for folate are linked to the prevention of megaloblastic anemia and neural tube defects (NTDs).^{33,35}

When micronutrient intakes are inadequate, suboptimal cellular/physiological functions can occur in advance of developing a classic symptomatic deficiency condition.³³ For example, inadequate vitamin A stores are associated with immunodeficiency. Several other micronutrients in addition to vitamin A play important roles in innate and adaptive immunity (eg, vitamin D), and inadequacies impair normal immune function, which may increase the risk of infectious diseases and cancer.^{33,35} Potassium inadequacies are associated with hypertension and increased risk of myocardial infarction and stroke.^{33,36} Inadequacies in intakes of folate and vitamin C are associated with biomarkers indicating an increased risk for hyperhomocysteinemia, chromosome breakage, chronic inflammation, and oxidative damage.^{33,37}

Although micronutrient inadequacies are associated with risk of deficiency and impaired biological functioning, more research is necessary to establish clear dose–response relationships between biological functional status and health outcomes, taking into consideration interindividual and regional differences in diet, lifestyle, environment, and genetic variants. This effort could also clarify apparent increases in function beyond those associated with deficiencies and inadequacies, as suggested by studies of higher or “optimal” doses of vitamins C and D showing apparent improvements in physiological functioning and risk reduction for age-related chronic diseases.^{38–43}

3. Achieving micronutrient intake levels on a population-wide and individual basis that are consistent with established reference values should be an explicit public health goal.

A+: 64%; **A:** 36%

Human health requires complete and balanced nutritional intake; however, inadequacies in vitamin and mineral intakes have been widely described, not only in impoverished and undernourished populations^{44,45} but also in developed countries with apparently sufficient resources.⁴⁶ Micronutrients are available via the diet, food fortification, supplementation, or a combination of these approaches,⁴⁷ with dietary micronutrient intake being influenced by numerous factors that change over time.⁴⁴

Global recommendations for micronutrient intake include DRIs, which are developed by the US National Academy of Medicine⁴⁸ and Health Canada,¹² and Dietary Reference Values developed by the UK

Scientific Advisory Committee on Nutrition⁴⁹ and the European Union Food Safety Authority,⁵⁰ and Nutrient Reference Values developed for Australia and New Zealand.⁵¹ Technical support documents provide the scientific evidence for recommendations of each micronutrient and reference values developed to direct public policy decisions.^{52,53} The World Health Organization⁴⁴ and the Food and Agriculture Organization of the United Nations⁵⁴ recognize the critical role that governments play in setting national policies to promote adequate nutrient intake and protect public health. Support for nutrition guidelines in public policy is also expressed in the United Nations Sustainable Development Goals to improve nutrition and protect good health and well-being.⁵⁵

Setting public health goals to achieve recommended micronutrient intakes at individual and population levels presents challenges with implementation and monitoring. In setting public policy, these efforts should appreciate existing knowledge gaps for some micronutrient recommendations and recognize the diversity of individuals and populations and their respective dietary requirements. Consistent with current practices, meeting micronutrient needs for individuals and populations often requires a combination of improving dietary patterns, fortifying staple foods, and supplementing the diet with products such as MVMS. Notably, in some regional programs, focus on ensuring adequate energy intakes for growth and development ignores the risk of “hidden hunger,” which results from inadequate micronutrient intakes from low-quality diets and adversely affects global health.⁵⁶

4. Using a daily MVMS is one way to help provide the recommended intake levels of many micronutrients that are necessary for maintaining health through supporting the function of specific metabolic pathways, cells, organs, or other physiological systems.

A+: 43%; A: 57%

Due to the difficulty in establishing the effect of MVMS ingredients generally on a given health outcome, to investigate the role of supplements in influencing metabolic and physiological systems, evidence was explored via selected illustrations of priority areas within public health nutrition. These areas included: (1) folate in early life; (2) B vitamins and

cognitive health in aging; and (3) vitamin D and health.

The evidence linking inadequate folate status with NTDs is conclusive, and other effects of this B vitamin (and metabolically interrelated B vitamins) throughout the life cycle are becoming evident.⁵⁷ Achieving sufficient folate status and biomarkers thereof is challenging because natural food folates are inherently unstable, have limited bioavailability, and can undergo significant losses before ingestion.⁵⁸ In contrast, folic acid (ie, the vitamin form found in supplements and fortified food) can overcome these limitations, as it is stable and highly bioavailable. Therefore, improved folate biomarker status is more easily achieved by consuming the vitamin through supplements and fortified food compared with equivalent intakes of folate from natural food sources.^{59,60} In the absence of folic acid fortification or supplementation, the average diet does not achieve adequate folate status. Thus, in regions without mandatory folic acid fortification (eg, European Union countries), poor compliance with recommendations to promote folic acid supplements as a policy to prevent NTDs is reflected in evidence showing no change in the prevalence of NTDs over the 20 years since the Medical Research Council Vitamin Study demonstrated that folic acid prevents recurrence of NTDs.^{61–63} Furthermore, using folic acid-containing MVMS is proven to reduce the incidence of first occurrence of NTDs⁶⁴ and is recommended globally before and in early pregnancy.^{62,65}

Beyond NTDs, supplements containing folate-related B vitamins (ie, B₁₂, B₆, riboflavin) may have additional benefits, as they are required for normal folate recycling within one-carbon metabolism. Important gene–nutrient interactions are also recognized in these metabolic pathways, and recent research suggests their impacts on health, such as a novel interaction of riboflavin with the MTHFR gene that affects blood pressure regulation.⁶⁶

Nutritional approaches to slow the progression of age-related cognitive decline are of increasing public health interest due to the growing proportion of elderly people developing these symptoms around the world. Although certain dietary patterns (eg, Mediterranean diet) and specific nutrients (eg, *n*-3 polyunsaturated fatty acids and polyphenols) seem to be associated with cognitive health in aging,^{67–69} the

totality of evidence from observational studies and RCTs seems strongest in supporting roles for folate, vitamin B₁₂, and vitamin B₆ through mechanisms related to B vitamin–dependent one-carbon metabolism, a network of pathways essential for healthy cellular functioning, including in the brain.^{34,70–72} Recent evidence shows that elderly people with lower B vitamin intake and status have higher rates of cognitive decline.⁷³ However, additional research is needed to demonstrate that intervention with B vitamin supplements can significantly affect cognitive functioning in older adults.⁷⁴

Vitamin D supplementation can reduce the risk of deficiency (serum 25[OH]D < 30 nmol/L) and insufficiency (30–50 nmol/L), which are prevalent globally.^{75,76} Vitamin D is essential for bone and muscle function and immune regulation. The preventive effect of vitamin D in osteoporosis is well established⁷⁷; however, the evidence in other areas, although provocative, is less clear. Promising observational evidence supports the role of vitamin D in cognitive health in older adults, but RCTs to date have not confirmed this effect.⁷⁸ Recent evidence from a 4-year randomized trial of vitamin D plus calcium supplementation in postmenopausal women did not reduce the incidence of cancer.⁷⁹ The results of 3 large RCTs from the United States, Australia, and Finland investigating vitamin D supplementation in relation to cardiovascular disease (CVD) and cancer are expected in the coming years.^{80–82}

5. On a population basis, use of daily MVMS reduces the prevalence of inadequate intakes of the micronutrients they contain.

A+: 86%; A: 14%

A MEDLINE search was conducted (1946 to May 2017) to obtain evidence regarding the impact of supplementation on nutrient inadequacies, using the following terms: “nutrition surveys” or “diet surveys” or “nutrient adequacy” combined with “dietary supplements” or “multivitamin supplements.” Among the 634 citations retrieved, 13 reported intakes of multiple micronutrients by supplement use in national population-based samples.

Surveys conducted in the United States, Canada, Korea, Germany, and Mexico were identified; in several countries, multiple publications were available.^{10,11,29–31,83–91} These studies included adults (n = 10) and/or children (n = 7), and most compared total

nutrient intakes of supplement users and nonusers. These surveys consistently revealed that supplement users have higher micronutrient intakes and/or lower prevalence of inadequacies or intakes below recommended levels.

Two studies analyzing US National Health and Nutrition Examination Survey datasets specifically assessed the population prevalence of nutrient inadequacies with and without MVMS. Wallace et al¹⁰ found that MVMS use (≥1 day per month), compared with nonuse, significantly reduced the prevalence of inadequate intakes (assessed as nonoverlapping 95% confidence intervals [CIs]) of vitamins A, C, D, and E; calcium; and magnesium. For other micronutrients (eg, thiamine, riboflavin), the prevalence of inadequacy was lower with MVMS use but not statistically significant, in part because of the very low prevalence of inadequacies regardless of supplementation. Blumberg et al¹¹ found that in relation to intake from food alone, MVMS use at any frequency was associated with a lower prevalence of inadequacies (*P* < 0.01) for 15 of the 17 micronutrients examined. Significant (*P* < 0.01) increases in the prevalence of intakes exceeding the UL for 7 micronutrients were observed, but the prevalence was ≤4% for any micronutrient. Except for calcium, magnesium, and vitamin D, the most frequent category of MVMS use (≥21 days per month) virtually eliminated inadequacies of the nutrients examined. Furthermore, MVMS use was associated with significantly lower odds ratios (ORs) of deficiency for all the examined nutrient biomarkers except for iron.

6. Based on current knowledge, the long-term use of MVMS with an amount not exceeding the UL is safe in healthy adults.

A+: 71%; A: 29%

The safety of micronutrients is dependent on their intakes falling between recommended levels and ULs. In an analysis of data from the US National Health and Nutrition Examination Survey (N = 16,444), MVMS reduced the percentage of the population with nutrient intakes below the Estimated Average Requirement but did not cause excess intake.¹⁰ In users of MVMS, the prevalence of those exceeding the UL was 1.7% for retinol and 2.5% for folic acid. Indeed, even if fortified food and beverages are considered, it seems unlikely that intakes will exceed the UL in the

long term. For determining safety, both the amount supplied and the length of use within different age groups should be determined.

Few studies exist that document long-term use and specifically evaluate adverse events (AEs). A review by Simpson et al⁹² reported 6 studies of MVMS that used biological safety data from children and adults and reported no clinically meaningful AEs or abnormal blood tests related to toxicity. AE data from 157 children and adults revealed only minor, transitory reports of headache and nausea. One study that directly compared the safety of supplements and conventional psychiatric medications found no clinically meaningful abnormal laboratory values among its 88 pediatric and adult subjects. The supplement group experienced significantly fewer AEs ($P \leq 0.026$) and less weight gain ($P < 0.0001$). In the Physicians' Health Study (PHS) II, the only RCT that has addressed the safety of long-term MVMS use versus placebo, no significant differences were found on gastrointestinal symptoms (eg, peptic ulcer, constipation, diarrhea, gastritis, nausea), fatigue, drowsiness, skin discoloration, or migraine.⁹³ A systematic review of RCTs by Biesalski and Tinz⁹⁴ addressed safety of MVMS; 9 studies evaluated use of MVMS in pregnant women and healthy adults, and 6 studies explicitly assessed AEs in the elderly. Only minor AEs (eg, unspecific gastrointestinal symptoms) were reported, and there were no significant differences between groups. Based on current knowledge, the long-term use of MVMS (>10 years) with doses not exceeding ULs seems to be safe.

7. The evidence that long-term use of MVMS contributes to a reduction in the risk of some chronic diseases is insufficient to support the use of MVMS in the primary prevention of these diseases.

A+: 64%; A: 29%; U: 7%

In the 21st century, the global burden of disease and associated mortality will continue to be driven primarily by CMCs.⁹⁵ The World Health Organization's Global Action Plan for the Prevention and Control of Noncommunicable Diseases proposes policies to increase consumption of fresh fruits and vegetables and reduce energy-rich, micronutrient-poor foods.⁹⁶ Evidence from basic research and observational studies indicates that dietary factors, including micronutrients, are key components for preventing the development of CMCs, including some forms of cancer.⁹⁷

In observational studies, the relationship between the total intake of micronutrients at dietary levels and the incidence of CMCs (eg, cancer, CVD, age-related eye diseases) has been shown primarily to be null, and in some instances, positive and even negative associations were reported.⁹⁸ In a meta-analysis of 13 cohort studies conducted by Park et al,⁹⁹ an aggregate analysis of individuals enrolled in 10 studies using MVMS for 7 to 20 years found a decreased risk of colon cancer (relative risk [RR], 0.88; 95% CI, 0.81–0.96) versus nonusers. A meta-analysis of cohort studies conducted by Ye and Song¹⁰⁰ found a modest risk reduction in CVD associated with higher intakes of vitamins C and E and β -carotene. Results from the prospective Nurses' Health Study showed that long-term use (>15 years) of MVMS (with folic acid) was associated with a decreased risk of colon cancer (RR, 0.25; 95% CI, 0.13–0.51) versus nonuse.¹⁰¹ A long-term prospective cohort study of subjects enrolled in PHS I found no association between MVMS use and most assessed cardiovascular outcomes, although a 14% decrease was observed in cardiovascular revascularization risk (hazard ratio [HR], 0.86; 95% CI, 0.75–0.98) versus nonuse. In addition, a self-reported history of ≥ 20 years' MVMS use was associated with a 44% reduction in risk for CVD (HR, 0.56; 95% CI, 0.35–0.90).¹⁰²

Similar to observational studies, RCTs of MVMS use and chronic disease risk have shown mixed results. A meta-analysis of RCTs conducted by Fortman et al¹⁰³ indicated that long-term MVMS use (11.2–12.5 years) reduced the incidence of cancer (RR, 0.94; 95% CI, 0.89–1.00) versus placebo. Two studies included in this meta-analysis (PHS II⁹³ and Supplementation en Vitamines et Mineraux Antioxydants [SU.VI.MAX]¹⁰⁴) individually found a reduction in cancer risk and mortality in men. In PHS II, a significant 8% reduction in total cancer incidence was observed versus placebo (HR, 0.92; 95% CI, 0.86–0.998), as well as an 18% reduction in total cancer incidence in men aged ≥ 70 years (HR, 0.82; 95% CI, 0.72–0.93).⁹³ In the total population, the risk for cancer development was 12% lower with MVMS use compared with placebo when prostate cancer was excluded (HR, 0.88; 95% CI, 0.79–0.98). The greatest total cancer risk reduction was observed in the total population of men with baseline cancer histories (HR, 0.73; 95% CI, 0.56–0.96), but no

benefit was observed for specific cancer types (ie, prostate, lung, colorectal, and pancreatic, for which PHS II was insufficiently powered).

Another meta-analysis by Fortman et al¹⁰³ reported no significant effect of MVMS for reducing CVD risk (RR, 1.02; 95% CI, 0.94–1.10) based on the results of PHS II and SU.VI.MAX. Other MVMS meta-analyses that evaluated CVD have also primarily reported null outcomes. Six reviews or meta-analyses, principally of RCTs, that evaluated combinations of vitamins C and E, β -carotene, and selenium found no effect on the primary or secondary prevention of CVD.^{105–110} Similarly, SU.VI.MAX, which included 13,017 French men and women who received a combination of vitamins C and E, β -carotene, selenium, and zinc, found no significant overall benefit versus placebo in ischemic CVD (RR, 0.97; 95% CI, 0.77–1.20).¹¹¹ However, the overall mortality risk was significantly lower in men (RR, 0.63; 95% CI, 0.42–0.93) but not in women (RR, 1.03; 95% CI, 0.64–1.63). In 2 analyses from PHS II, no reduction in major cardiovascular events was observed with higher doses of vitamin C or E for 8 years or MVMS for 11 years,^{112,113} but a significant reduction in myocardial infarction death (HR, 0.61; 95% CI, 0.38–0.995) was observed with the MVMS.¹¹³

PHS II also evaluated subjects on age-related eye disease outcomes and reported a reduction in cataract development (HR, 0.91; 95% CI, 0.83–0.99) and cataract surgeries (HR, 0.89; 95% CI, 0.80–0.99) versus placebo.¹¹⁴ Similarly, in the Age-Related Eye Disease Study (AREDS), a risk reduction for any lens (OR, 0.88; 95% CI, 0.79–0.98) or nuclear opacity (OR, 0.78; 95% CI, 0.68–0.89) was observed in users of MVMS versus nonusers.¹¹⁵ The Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataract administered MVMS for 9 years (N = 1020) and reported a decrease in nuclear opacity progression among a population with early or no cataracts.¹¹⁶ The AREDS supplement containing vitamins C and E plus zinc, copper, and β -carotene reduced the risk for loss of visual acuity and progression to advanced age-related macular degeneration (ARMD) versus placebo.¹¹⁷

Despite the promising data in this area, several observational studies and RCTs have failed to show that MVMS decrease the risk of CMCs. However, some studies conducted with supra-dietary doses of individual micronutrients have indicated the potential

for harm (eg, an increased risk of lung cancer with 20 mg β -carotene in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study¹¹⁸ and an association between high vitamin B₆ single supplements and lung cancer in the Vitamins and Lifestyle Study cohort¹¹⁹). Long-term use of MVMS at doses approximating recommended intakes has been shown to be safe.⁹⁴ The totality of these data, therefore, is insufficient to support using MVMS for CMC prevention.

8. MVMS use in populations with inadequate intakes or increased needs of micronutrients can provide benefits to apparently healthy individuals, including children, pregnant women, and older adults.

A+: 36%; A: 50%; U: 14%

Searches for systematic reviews and meta-analyses published in the past 5 years were conducted by using the following criteria: population (adults, children, pregnant women); interventions (MVMS, vitamin D, iron at supplement doses); comparisons (no MVMS); and outcomes (growth, pregnancy outcomes, intelligence/cognition, psychological features, cataracts, safety).

Children

Administration of MVMS and supplements containing vitamin A and zinc can improve linear growth in school-aged children and cognitive performance in children likely to be deficient in micronutrients but otherwise healthy.^{120,121} A meta-analysis by Roberts and Stein¹²⁰ examined baseline height-for-age *z* score, subject age, nutrient dose, and study duration for heterogeneity in 69 RCTs, most of which were conducted in low- and middle-income countries. Zinc (17 studies and 19 datasets; mean effect size [ES], 0.15; 95% CI, 0.06–0.24), vitamin A (5 studies and 16 datasets; mean ES, 0.05; 95% CI, 0.01–0.09), and ≥ 2 of any micronutrients (17 studies; mean ES, 0.26; 95% CI, 0.13–0.39) had positive effects on linear growth, but iron, calcium, iodine, and food-based interventions did not. Baseline age, study duration, and dose were not predictors of ES for any nutrient examined. A systematic review of 19 RCTs by Lam and Lawlis¹²¹ conducted with data primarily from developing countries and children experiencing deficiencies found that micronutrients positively affected fluid intelligence (ie, problem solving, logic). No meta-analysis was possible owing to differences in reporting. No consistent effect on

crystallized intelligence (memory), attention, or school performance was found. An examination of MVMS use in infants was not conducted.

Healthy Adults

A meta-analysis of 8 MVMS RCTs conducted by Long and Benton¹²² reported a reduction in minor psychiatric symptoms among healthy adults. Perceived stress (standard mean difference [SMD], 0.35; 95% CI, 0.47–0.22; $P = 0.001$), mild psychiatric symptoms (SMD, 0.30; 95% CI, 0.43–0.18; $P = 0.001$), and subclinical anxiety (SMD, 0.32; 95% CI, 0.48–0.16; $P < 0.001$) were reduced compared with placebo, but subclinical depression was not (SMD, 0.20; 95% CI, 0.42–0.03; $P = 0.089$). Fatigue (SMD, 0.27; 95% CI, 0.40–0.146; $P < 0.001$) and confusion (SMD, 0.225; 95% CI, 0.38–0.07; $P < 0.003$) were also reduced compared with placebo.

Pregnant and Breastfeeding Women

Two Cochrane reviews examined MVMS versus iron and/or folic acid supplementation alone during pregnancy. Haider and Bhutta¹²³ identified 19 RCTs conducted in predominantly low- and middle-income countries (United Kingdom, 2 studies; France, 1 study). A significant reduction in low-birth-weight infants was found with MVMS versus iron and/or folic acid (RR, 0.88; 95% CI, 0.85–0.91), but no differences were found in preterm births or stillbirths, neonatal death, miscarriage, or operative delivery risk. Balogun et al¹²⁴ indicated that taking any vitamin supplements before or during early pregnancy did not decrease miscarriage rates.

A meta-analysis of 31 observational studies and 4 RCTs conducted by Wolf et al¹²⁵ evaluated the effect of MVMS on pregnancy outcomes in developed countries. Using the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) criteria, the quality of evidence was assessed as low or very low for all outcomes except for NTD recurrence, for which a moderate benefit was found. MVMS use did not change the risk for preterm birth (RR, 0.84; 95% CI, 0.69–1.03). However, the risk of small for gestational age infants (RR, 0.77; 95% CI, 0.63–0.93), NTDs (RR, 0.67; 95% CI, 0.52–0.87), cardiovascular defects (RR, 0.83; 95% CI, 0.70–0.98), urinary tract defects (RR, 0.60; 95% CI, 0.46–0.78), and limb deficiencies (RR, 0.68; 95% CI, 0.52–0.89) decreased.

Vitamin D alone (200–2000 IU/d) or single doses of 60,000 to 600,000 IU were examined in a Cochrane review conducted by De-Regil et al.¹²⁶ Data from 477 women (3 RCTs) indicate that vitamin D supplementation during pregnancy reduces the incidence of preterm birth (8.9%) versus no intervention or placebo (15.5%; RR, 0.36; 95% CI, 0.14–0.93; moderate quality). Data from 493 women (3 RCTs; 1 of the aforementioned trials and 2 others) also revealed that vitamin D supplementation during pregnancy reduces the frequency of having a low-birth-weight infant (< 2500 g) compared with no intervention or placebo (RR, 0.40; 95% CI, 0.24–0.67; moderate quality).

Calcium supplementation alone has also been studied at doses typically formulated in MVMS. A Cochrane review by Hofmeyr et al¹²⁷ found a small effect of calcium supplementation on pre-eclampsia risk, but these studies were small and the risk for hemolysis, elevated liver enzyme levels, and low platelets increased with supplementation.

Older Adults

A Cochrane review that examined vitamin D supplementation versus placebo or no intervention found a decrease in mortality when all 56 trials were analyzed together (5920 of 47,472 [12.5%] vs 6077 of 47,814 [12.7%]; RR, 0.97; 95% CI, 0.94–0.99; $P = 0.02$; $I^2 = 0\%$).¹²⁸ However, these studies were of low to moderate quality due to considerable attrition and the relatively short duration of some studies, and a sensitivity analysis suggested that the result should be considered with caution. A meta-analysis of 24 RCTs by Forbes et al¹²⁹ involving interventions including B vitamins, vitamin E, or omega-3 fatty acids evaluated cognitive function and found no statistically significant effect on Mini-Mental State Examination or digit span forward scores. There is evidence, primarily from cohort studies, that MVMS may reduce cataract risk.¹³⁰

9. Some individuals with CMCs experience nutritional deficiencies and/or inadequacies that can be prevented and treated with adequate dietary management and/or the use of MVMS.

A+: 86%; A: 14%

The evidence reviewed here included studies identified through a PubMed search; diverse ranges of search terms related to MVMS and some specific CMCs were included.

Age-related Eye Diseases

In the AREDS 2 study, 1 supplement replaced β -carotene with lutein and zeaxanthin, and a significant benefit ($P = 0.01$) was observed in slowing the progression to advanced ARMD in patients with low dietary intake of these carotenoids and either current bilateral large drusen or large drusen in 1 eye and advanced ARMD in the other eye.¹³¹ In the Lutein Antioxidant Supplementation Trial, subjects with existing atrophic ARMD who received lutein alone or combined with antioxidants showed improvements in visual function after 1 year.¹³²

Women's Health

Female infertility treatment has been shown to improve with micronutrient supplementation, particularly with combinations of folic acid; vitamins B₆, C, and D; iodine; selenium; iron; and/or omega-3 fatty acids.¹³³ In a small pilot study, MVMS have shown better results versus folic acid alone in ovulation induction among women undergoing fertility treatment.¹³⁴ Osteopenia and osteoporosis are prevalent in postmenopausal women, and optimization of vitamin D and calcium intake is recommended for managing individuals with these conditions due to their role in maintaining bone mineral density and reducing the risk of falling^{135,136}; however, those at highest risk of subsequent fractures will likely require additional pharmacologic and nonpharmacologic treatments.

Obesity

Deficiencies or inadequacies in vitamin B₆, C, D, and E can occur among obese individuals,¹³⁷ and many weight-loss diets can cause micronutrient inadequacies.¹³⁸ Furthermore, body mass index has been shown to be associated with poor folate status in nonpregnant women of childbearing age, suggesting that obesity may modify folate metabolism.¹³⁹ Bariatric surgery can also cause or exacerbate micronutrient deficiencies, especially vitamin B₁₂ and iron, and this risk is higher with gastric bypass procedures that involve food malabsorption.¹⁴⁰ After bariatric surgery (particularly Roux-en-Y gastric bypass), dietary patterns do not improve to an ideal level.¹⁴¹ Vitamin D deficiency after bariatric surgery is common and must be treated to reduce osteoporosis risk.¹⁴² Preventing micronutrient deficiencies is believed to be critical to bariatric surgery success.¹⁴³ This scenario may be particularly important for obese

women of childbearing potential who may be at an increased risk for key nutrient deficiencies and inadequacies related to negative pregnancy outcomes (eg, NTDs).¹⁴⁴ Although most patients receive post-bariatric-surgery MVMS and report improvements in their nutritional status and prevention of anemia, there is a large disparity in the prevalence of this practice.^{145,146} Furthermore, MVMS may not provide adequate nutritional support,¹⁴⁷ and individual supplements at higher doses may be necessary for certain individuals.

Type 2 Diabetes Mellitus

Levels of vitamins A, C, and E, thiamine, pyridoxine, and biotin can be reduced in type 2 diabetes mellitus (T2DM), and metformin treatment impairs the bioavailability of vitamin B₁₂ and folic acid.^{148,149} Metformin also negatively affects vitamin B₁₂ status in patients with polycystic ovary syndrome.¹⁵⁰ Most MVMS studies in patients with diabetes have shown inconclusive results on disease progression and its sequelae, although MVMS improved micronutrient status.¹⁴⁸ However, a meta-analysis of RCTs that evaluated magnesium supplementation reported improvements in insulin resistance.¹⁵¹ An RCT conducted in patients with T2DM who received MVMS with a zinc supplement reported improvements in glycemic control and lipid profile versus placebo.¹⁵²

DISCUSSION

Health care research and policy development are primarily driven by the paradigm of evidence-based medicine. However, certain facets of nutrition research regarding health promotion and disease prevention, as implemented, do not fit well within this context; in particular, reliance on RCTs as the “gold standard” for evidence-based policy.^{153–156} For example, although nutritional status at baseline and dietary variability during the RCTs (especially when these factors are not assessed) can significantly affect the interpretation of results, these are often overlooked in the analysis. In addition, dietary supplements, MVMS in particular, typically provide doses that approximate recommended intake levels and would only produce modest changes, albeit with potentially large public health benefits. Inappropriately conflating expectations regarding health outcomes of nutritional interventions can lead to confusion among HCPs

and incorrect conclusions, and findings arising from the research can often be misrepresented in the lay media, resulting in misunderstandings by the public.

The conflicting evidence associated with the use and benefits of MVMS helps reveal several gaps in our knowledge base and provides a rationale for convening this consensus panel. As suggested in these summaries, although the essentiality of micronutrients in human biology and health is well understood, additional research is necessary to fully elucidate the role of MVMS for maintaining and promoting health and preventing CMCs. Despite certain limitations associated with various research approaches in several of the studies described here, there is a clear indication that, within the general population, appropriately formulated MVMS can safely provide essential micronutrients to help individuals achieve recommended intake levels.^{28,94} However, when recommending any dietary supplement to a patient, it is important that HCPs consider individual factors, including dietary micronutrient intakes, to avoid exceeding ULs of nutrients that may cause adverse effects when overconsumed. As noted earlier, MVMS should not be viewed as substitutes for a balanced diet but should be recommended, in addition to other advice for a healthy lifestyle, to ensure adequate micronutrient intake and status.

CONCLUSIONS

This consensus panel has indicated that MVMS can improve the micronutrient intake and, hence, the nutritional status of individuals presenting with deficiencies and inadequacies, including those with CMCs. However, the effect of MVMS on the primary prevention of CMCs is presently inconclusive, despite some modest yet promising results from RCTs. Importantly, there is a clear indication that the long-term use of MVMS formulated with doses that do not exceed ULs is safe; however, additional research is necessary to fully define the benefits of MVMS for health promotion and disease prevention. Consumers and clinicians should therefore consider the risks of deficiencies and the potential benefits of supplementation. Given the relatively low cost and established safety of MVMS, as well as the essentiality of adequate micronutrient status for human biology and good health, HCPs should assess their patients' dietary needs and risk of micronutrient inadequacies and consider intervening with MVMS for their at-risk patients.

CONFLICTS OF INTEREST

At the direction of the co-chairs (Drs. Blumberg and Cena), after an initial discussion with Pfizer Consumer Healthcare regarding the project, the company played no role in the Delphi process or preparation of this report but did provide funding for the organizational aspects of the Delphi process, the panel meeting in Philadelphia, and the contributions of Peloton Advantage, which provided overall coordination of the process and editorial assistance.

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Dr. Blumberg acts as a consultant to companies that manufacture or market dietary supplements, including service on the Nutrition Advisory Committee at Pfizer Consumer Healthcare. Dr. Cena acts as a consultant to companies that manufacture or market dietary supplements, including Pfizer Consumer Healthcare. Dr. Biesalski acts as a consultant for Ratiopharm, a company that manufactures dietary supplements. Dr. Frei acts as a consultant for Pfizer Consumer Healthcare and DSM Nutritional Products. Dr. Hwalla acts as a consultant for Pfizer Consumer Healthcare. Dr. Lategan-Potgieter has received honoraria from Pfizer Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Drs. Blumberg and Cena co-chaired the consensus panel meetings; they directed and participated in the development of the statements, the consensus process, drafting of evidence reviews, and preparation of the manuscript. All the authors contributed to the development of the manuscript through reviews, revisions, and approval of the final version.

SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.clinthera.2018.02.014>.

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